N-Alkoxy Analogues of 3,4,5-Trihydroxypiperidine

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Two practical procedures are described for the synthesis of the *N*-alkoxy analogues of 3,4,5-trihydroxypiperidine. The key feature of these methods is the intramolecular *N*-cyclization of hydroxylamine derivatives which are readily obtained from the reduction of the corresponding oximes. One method is to reductively hydroxyaminate an aldehyde group in the presence of a primary tosylated alcohol which is subsequently cyclized in situ upon neutralization. The intramolecular Mitsunobu coupling of a hydroxylamine with a primary alcohol proved useful for the preparation of compounds which contained the trans diol structure.

Introduction

Naturally occurring polyhydroxylated piperidine alkaloids have attracted much attention due to their ability to act as glycosidase inhibitors.[1] The inhibitory properties of these alkaloides hold great therapeutic potential for the treatment of infectious diseases,[2] and recent progress in this area has prompted considerable interest in the structure−function relationship for polyhydroxylated piperidines. A plethora of synthetic analogues, including 1-deoxynojirimycin (**1**) and *n*-butylnojirimycin (**2**) (Figure 1), have been prepared and evaluated for glycosidase inhibition and for anticancer, antidiabetic, and antiviral (anti-HIV) activities.[3] The majority of the synthetic analogues, which are designed to mimic the transition states of glycoprotein processing, maintain the replacement of the glycoside ring oxygen with a basic piperidinyl nitrogen atom. We reasoned that the direct attachment of an electron-withdrawing alkoxy group to the nitrogen in iminoglycosides can potentially bridge two units of saccharides for a unique class of multisubstrate glycosidase inhibitors.

We wish to report an efficient route to the *N*-alkoxy-3,4,5-trihydroxypiperidines (**3**−**6**) based on tandem reductive cyclization (Figure 1). The four possible isomers for this structure were prepared to study the influence of the absolute stereochemical configurations of individual hydroxyl groups on inhibitory potency and the contribution of each hydroxyl group in the glycosides to the free energy of binding with enzyme.[4] It was also of interest to prepare diastereoisomers of *N*-alkoxytrihydroxypiperidines in order to develop potential inhibitors for variant glycosidases. The specific inhibition of a variety of glycosidases appears to require structural similarity between inhibitor and natural substrate. For example, deoxynojrimycin has been shown to be a superior inhibitor of glucosidase-I compared to the mannose analogue, deoxymannojirimycin.[5]

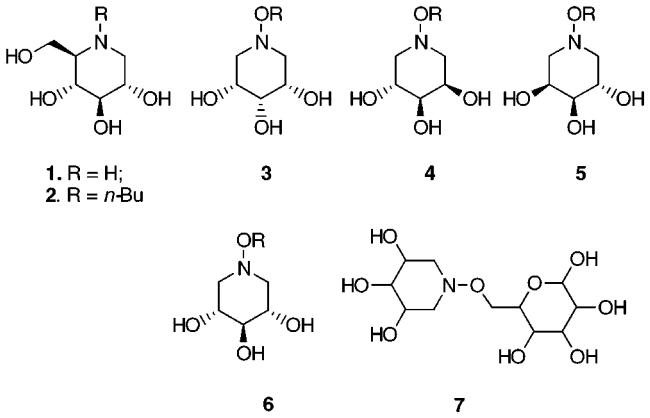

Figure 1.

We also report a detailed procedure for the preparation of disaccharide analogues (e.g., **7**) as a demonstration of the efficiency of the hydroxylamine cyclization methods for the construction of structurally diverse piperidine derivatives. The N−O moiety of **7**, in addition to serving as the pivotal center of a transition-state analog-based inhibitor, also served as a handle for coupling the iminosugar to a saccharide unit. These compounds and related polysaccharide analogues are postulated to resemble the structural feature of both donor and acceptor moieties of enzymatic substrates.[6]

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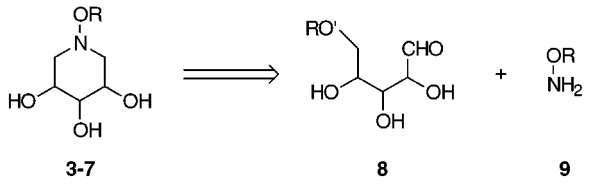
Scheme 1



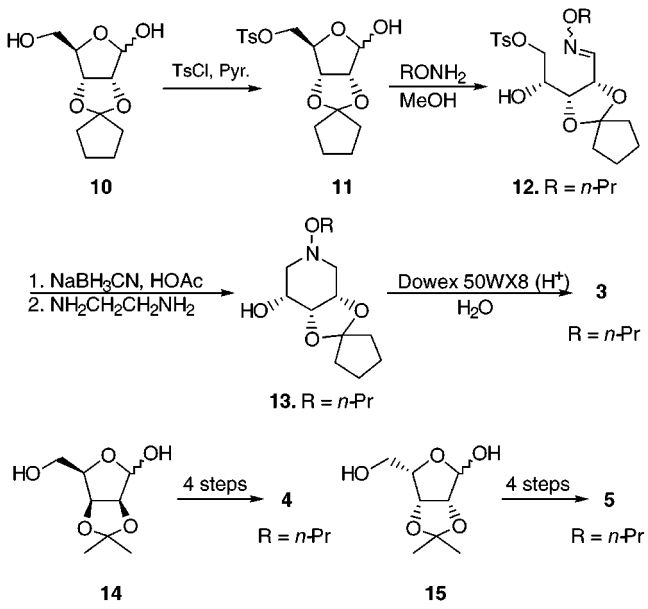
Results and Discussion

Structural analysis of compounds **3**−**7** revealed that the polyhydroxylated carbons of the piperidine rings corresponded to those of the pentose derivatives **8** (Scheme 1). A practical approach to the desired compounds **3**−**7** would be the connection of both terminal carbons of **8** to hydroxylamine derivatives **9**. One connection could be achieved via the reductive amination of **8** and **9**, and another by an intramolecular S_N cyclization of the resulting hydroxylamine. This approach raised some interesting issues including the relative reactivities of the tosylate and aldehyde toward **9**. Another issue was the protection and deprotection of polyhydroxyl groups, an essential element if the nucleophilicity of hydroxyl moieties was comparable with that of the *N*-alkoxy-substituted nitrogen.

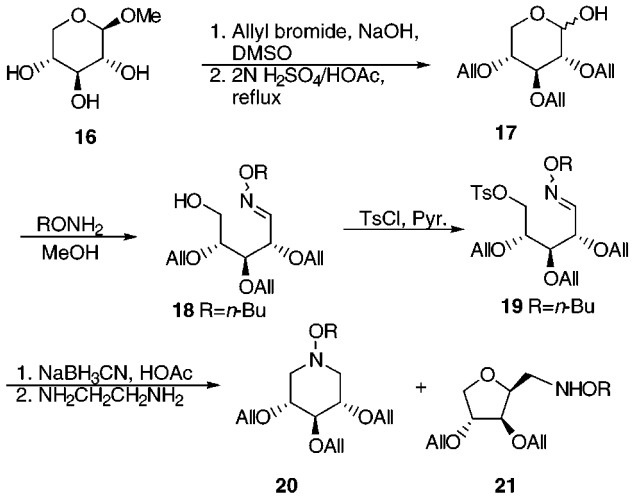
Ribose derivative **10** was used for the initial studies since it could be readily prepared from ribose by a literature procedure[7] and the primary hydroxyl group could be selectively tosylated to give **11**. The cyclic acetal in **11** was desired to protect the nucleophilic hydroxyl groups, thereby preventing their intramolecular displacement of the tosyl group. The treatment of **11** with propylhydroxylamine produced the corresponding oxime **12** in high yield,[8] and the tosyl group survived in the presence of *O*-propylhydroxylamine. The resulting oxime **12** was reduced by $NaBH_3CN$ under acidic conditions, and the subsequent neutralization by ethylenediamine afforded piperidine **13** which was easily converted to the final product **3**.[6] This efficient and practical method permitted the preparation of trihydroxypiperidine **3** from the readily available **10** in four synthetic operations with 64% overall yield, and the preparation of analogues **4** and **5** from 3-isopropylidenelyxoses **14** and **15**,[9] in 50% and 56% overall yields, respectively.

The difficulty of cyclic acetal formation posed by the trans diol in **16** required an acyclic alcohol-protecting group, and allyl ethers were tested (Scheme 3). D-Pyranoside **16** was alkylated under aqueous conditions[10] to give the corresponding triallylpyranoside which was hydrolyzed into corresponding triallyl xylose **17**. Acetal **17** was allowed to react with *O*-*n*-butylhydroxylamine to produce alcohol **18** which was then tosylated in pyridine to give **19** in 92% yield. When compound **19** was subjected to the same conditions of $NaBH_3CN$ reduction and ethylenediamine neutralization as described in Scheme 2, only about 40% of the desired product **20** was obtained. We also isolated the corresponding tetrahydrofuran

Scheme 2



Scheme 3



product **21** in 30% yield, which showed only two allyl groups and two nitrogen-connected protons. It is necessary to indicate that ethylenediamine neutralization of acetic acid is an exothermic reaction, raising the reaction temperature to 70 °C. This reaction temperature is needed for the conversion of **19** to compound **20**, but the intramolecular displacement of tosylate **19** by the allyl-protected oxygen at the three position also occurred to produce tetrahydrofuran **21**.

The Mitsunobu reaction was subsequently investigated for the intramolecular cyclization of primary alcohol and *N*-alkoxypiperidine (Scheme 4). Alcohol **22**, readily available from the reduction of oxime **18** in 95% yield, possesses a nucleophilic nitrogen center which may result in the desired Mitsunobu coupling.[11,12] The treatment

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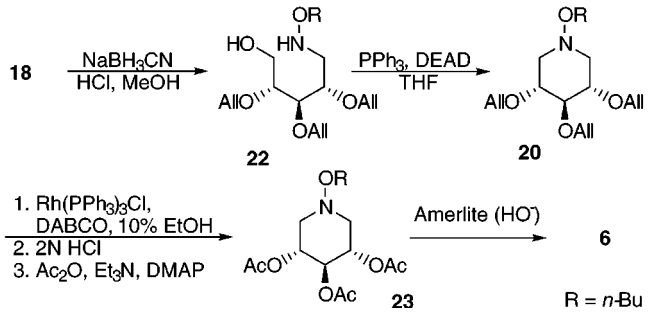
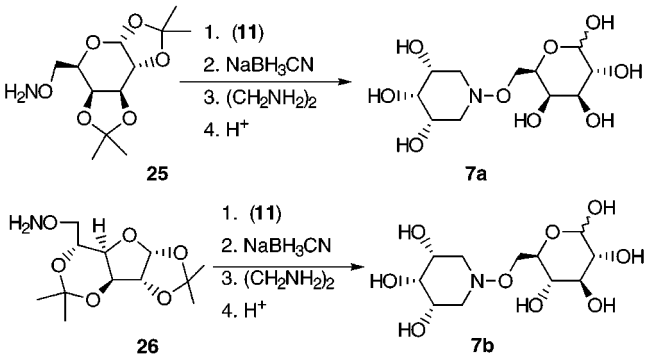
Scheme 4



Scheme 5



of **22** with triphenylphosphine and diethyl azodicarboxylate (DEAD), indeed, gave the *N*-cyclization product **20** as the only product in 75% yield. To our knowledge, this is the first example of the Mitsunobu-promoted cyclization of alcohols and *N*-alkylhydroxylamine derivatives.[12] It is also interesting to observe that the nitrogen of the hydroxylamine moiety of **22** becomes an improved nucleophile under Mitsunobu conditions. The final step to the desired product was to deprotect the *O*-alkyl groups of **20**, and we investigated Corey's method.[13] Treatment of **20** with rhodium chloride−triphenylphosphine complex promoted allyl migration to give the corresponding enol ether, and hydrolysis released the hydroxyl groups. The *N*-alkoxyamine group of **20** survived under these conditions, and the desired piperidine **6** was isolated via acetate **23** which was used as an intermediate for purification by silica gel chromatography.

We have also prepared pseudodisaccharides **7a** and **7b** by tandem reductive cyclization. The pseudodisaccharide **7a** was prepared from **11** and *O*-aminogalactose derivative **25**,[14] while **7b** was obtained from **11** and *O*-aminoglucose derivative **26**[14] as shown in Scheme 5. Additionally, the cyclization step could be accomplished by the Mitsunobu method (not shown here).

The present work succeeds in the efficient preparation of several *N*-alkoxylpiperidine analogues via two complementary approaches, which are based on the property of alkoxylamine. The stability of and unique reactivity of *N*-alkoxylamines allows for their selective coupling with appropriately protected saccharides to form the corresponding oximes, and after reduction, intramolecular S_N2 cyclizations can occur to give oxy−imine saccharides. The resulting molecules structurally resemble glycoside substrates and retain the electronic property of the pivotal piperidine nitrogen for mimicking the transition state of glycosyl hydrolysis. This work also demonstrates the usefulness of the Mitsunobu coupling of hydroxylamine and alcohol, a reaction with potential for the general synthesis of *N*-alkylhydroxylamines and through reduction for the corresponding amines.

Experimental Section

General details are as previously described.[15]

***N*-*n*-Propoxy-[3(e),4(a),5(e)]-3,4,5-trihydroxypiperidine (3).** A cold (0 °C) magnetically stirred solution of 2,3-*O*-cyclopentylideneribofuranose **10**[8] (2.85 g, 12.0 mmol) in anhydrous pyridine (10 mL) was treated with *p*-TsCl (3 g, 15.7 mmol), warmed to room temperature, and stirred for 5 h. After workup (ice water, Et_2O) and column chromatography purification (silica gel), intermediate **11** was isolated. A solution of *O*-*n*-propylhydroxylamine hydrochloride (270 mg, 2.42 mmol) in MeOH (10 mL) was treated with NaOH (90 mg, 2.25 mmol), stirred for 15 min, and transferred into the solution of **11** (690 mg, 1.86 mmol) in MeOH (10 mL) at room temperature. The reaction mixture was stirred overnight and then concentrated. Column chromatography purification (silica gel) gave oxime **12** (*E*/*Z* = 3/2) (615 mg, 1.44 mmol) in 75% overall yield: R_f = 0.27 (20% EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 8.3 Hz), 7.37 (0.6H, d, J = 6.5 Hz, *E*-isomer), 7.33 (2H, d, J = 8.3 Hz), 6.78 (0.4H, d, J = 5.5 Hz, *Z*-isomer), 5.14 (0.4H, dd, J = 5.4, 5.6 Hz, *Z*-isomer), 4.67 (0.6H, dd, J = 6.0, 7.1 Hz, *E*-isomer), 4.05 (6H, m), 2.64 (1H, br), 2.45 (3H, s), 1.70 (10H, m), 0.91 (3H, t, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 146.9, 145.4, 145.2, 133.1, 130.2, 128.4, 120.3, 120.1, 78.4, 77.1, 76.3, 75.3, 72.3, 71.9, 69.4, 68.3, 37.5, 37.0, 24.3, 23.8, 22.8, 22.2, 10.8. Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.18; H, 6.84; N, 3.28; S, 7.48. Found: C, 56.27; H, 6.89; N, 3.26; S, 7.42.

A solution of oxime **12** (560 mg, 1.31 mmol) in AcOH (5 mL) was treated with $NaBH_3CN$ (250 mg, 3.95 mmol) at room temperature and stirred until the reaction mixture became a homogeneous solution (ca. 1 h). To the above solution was added ethylenediamine (2 mL), and the resulting mixture was then stirred for 30 min. After workup (saturated $NaHCO_3$, EtOAc) and column chromatography purification (silica gel), piperidine **13** (265 mg, 1.03 mmol, 79%) was isolated: R_f = 0.50 (40% EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.22 (1H, m), 4.09 (1H, t, J = 4.0 Hz), 4.00 (1H, m), 3.55 (2H, t, J = 6.7 Hz), 3.16 (2H, m), 2.63 (3H, m), 1.74 (8H, m), 1.50 (2H, m), 0.86 (3H, t, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.0, 75.1, 74.1, 72.6, 65.9, 57.1, 56.2, 38.4, 38.1, 24.3, 24.0, 22.4, 11.1.

A solution of piperidine **13** (105 mg, 0.41 mmol) in water (10 mL) was treated with Dowex [50WX8 (H^+), 200 mg] at room temperature and stirred for 12 h prior to the addition of Et_3N (0.2 mL). The mixture was stirred for 5 h and then filtered through Celite. The filtrate was concentrated and azeotropically dried with benzene to give **3** (73 mg, 0.41 mmol, 100%): ^{1}H NMR (200 MHz, CD_3OD) δ 3.85 (3H, br), 3.62 (2H, t, J = 6.5 Hz), 3.04 (2H, br), 2.82 (2H, br), 1.56 (2H, m), 0.93 (3H, t, J = 7.4 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 74.8, 72.4, 67.8, 56.0, 23.4, 11.4. Anal. Calcd for $C_8H_{17}NO_4 \cdot 0.4H_2O$: C, 48.42; H, 9.04; N, 7.06. Found: C, 48.90; H, 8.63; N, 6.99.

***N*-*n*-Propoxy-[3*R*(a),4(e),5*R*(e)]-3,4,5-trihydroxypiperidine (4).** 41% overall yield; $[\alpha]^{25}_D$ = −6.0 (c = 10, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD) δ 4.07 (1H, m), 3.92 (1H, m), 3.73 (2H, t, J = 6.6 Hz), 3.55 (1H, br), 2.20−3.40 (4H, br), 1.56 (2H, m), 0.91 (3H, t, J = 7.4 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 76.7, 70.4, 70.1, 61.9, 24.4, 12.9. Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.15; H, 8.95; N, 7.17.

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(14) Compounds **25** and **26** were prepared from the corresponding carbohydrates bearing the unprotected 6-hydroxyl group. The Mitsunobu reaction of those derivatives with *N*-hydroxyphthalimide followed by the treatment with hydrazine in methanol produced the desired hydroxylamine products **25** and **26**. Grochowski, E.; Jurczak, J. *Carbohydr. Res.* **1976**, *50*, C15.

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***N*-*n*-Propoxy-[3*S*(e),4(e),5*S*(a)]-3,4,5-trihydroxypiperidine (5).** 37% overall yield; $[\alpha]^{25}_D = +6.0$ ($c = 10$, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD) δ 3.97 (1H, m), 3.83 (1H, m), 3.65 (2H, t, $J = 6.5$ Hz), 3.47 (1H, br), 2.20−3.40 (4H, br), 1.56 (2H, m), 0.92 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 76.7, 70.4, 70.1, 61.9, 24.4, 12.9. Anal. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.20; H, 9.03; N, 7.28.

6-*O*-{1-[3(e),4(a),5(e)]-3,4,5-Trihydroxypiperidinyl}-D-galactose (7a). 53% overall yield; $[\alpha]^{25}_D = +34.0$ ($c = 1$, H_2O); ^{1}H NMR (200 MHz, D_2O) δ 5.25 (1H, d, $J = 3.3$ Hz), 4.57 (1H, d, $J = 7.7$ Hz), 3.40−4.25 (9H, m), 2.80−3.20 (4H, br); ^{13}C NMR (50 MHz, D_2O) δ 99.4, 95.3, 75.8, 75.4, 74.8, 74.6, 74.1, 73.0, 72.9, 72.6, 72.2, 72.0, 71.3, 70.9, 68.6, 56.6. Anal. Calcd for $C_{11}H_{21}NO_9 \cdot 0.5H_2O$: C, 41.25; H, 6.92; N, 4.37. Found: C, 41.79; H, 6.80; N, 4.41.

6-*O*-{1-[3(e),4(a),5(e)]-3,4,5-Trihydroxypiperidinyl}-D-glucose (7b). 37% overall yield; $[\alpha]^{25}_D = +55.0$ ($c = 1$, H_2O); ^{1}H NMR (200 MHz, D_2O) δ 5.19 (1H, d, $J = 3.7$ Hz), 4.61 (1H, d, $J = 11.8$ Hz), 3.31−4.10 (9H, m), 3.20 (2H, br), 2.80 (2H, br); ^{13}C NMR (50 MHz, D_2O) δ 98.9, 95.0, 78.8, 77.1, 76.8, 75.8, 74.4, 73.7, 73.6, 73.0, 72.5, 68.6, 56.5. Anal. Calcd for $C_{11}H_{21}NO_9 \cdot H_2O$: C, 40.12; H, 7.03; N, 4.25. Found: C, 39.96; H, 6.86; N, 3.97.

(2*R*,3*S*,4*R*)-2,3,4-Tris(allyloxy)-5-tosyloxypentanal *O*-*n*-Butyloxime (19). A solution of methyl β-D-xylopyranoside (10 g, 61.0 mmol) in DMSO (150 mL) was treated with 50% aqueous NaOH (25 mL, 311 mmol) and stirred until it became homogeneous. Allyl bromide (23.8 mL, 274 mmol) was then added. The reaction mixture was stirred until no starting material was detected by TLC and extracted with Et_2O (2 × 250 mL). The combined organic layers were washed with water (2 × 100 mL), dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was dissolved in a solution of AcOH (100 mL) and 2 N sulfuric acid (100 mL), and the mixture was refluxed until no starting material was detected by TLC. After workup (saturated $NaHCO_3$, 250 mL; EtOAc, 2 × 250 mL) and column chromatography (silica gel) purification, triallylxylose **17** (13.0 g, 48.2 mmol) was isolated in 79% yield. $R_f = 0.50$ (40% EtOAc/petroleum ether).

A solution of *O*-*n*-butylhydroxylamine hydrochloride (315 mg, 2.51 mmol) in MeOH (10 mL) was treated with NaOH (100 mg, 2.51 mmol) and stirred for 15 min prior to the addition of a solution of **17** (565 mg, 2.09 mmol) in MeOH (10 mL) at room temperature. The mixture was stirred overnight, concentrated in vacuo, and purified by column chromatography (silica gel) to provide oxime **18** (710 mg, 2.08 mmol, 99%) as a mixture of two isomers ($E/Z = 3/1$): $R_f = 0.6$ (33% EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (0.75H, d, $J = 7.9$ Hz, *E* isomer), 6.82 (0.25H, d, $J = 6.0$ Hz, *Z* isomer), 5.85 (3H, m), 5.20 (6H, m), 3.60−4.20 (13H, m), 2.41 (1H, br), 1.63 (2H, m), 1.38 (2H, m), 0.92 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.5, 148.2, 135.3, 134.4, 117.9, 117.3, 80.8, 79.5, 76.8, 74.2, 72.5, 70.5, 62.0, 31.6, 19.5, 14.4. Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.34; H, 9.17; N, 4.05.

To the solution of oxime **18** (600 mg, 1.76 mmol), pyridine (3 mL), and several crystals of DMAP was added tosyl chloride (503 mg, 2.64 mmol). The reaction mixture was stirred for 1 h at room temperature. After workup (ice water, 100 mL; Et_2O, 2 × 100 mL) and column chromatography (silica gel) purification, oxime tosylate **19** (798 mg, 1.61 mmol) was isolated in 92% yield: $R_f = 0.60$ (20% EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (2H, d, $J = 7.3$ Hz), 7.33 (1H, d, $J = 6.9$ Hz), 7.23 (2H, d, $J = 7.3$ Hz), 5.78 (3H, m), 5.20 (6H, m), 4.33 (1H, dd, $J = 4.5$, 11.0 Hz), 4.12 (1H, t, $J = 6.9$ Hz), 4.03 (2H, t, $J = 6.2$ Hz), 4.02−4.10 (6H, m), 3.80 (2H, m), 3.52 (1H, t, $J = 4.5$ Hz), 2.42 (3H, s), 1.62 (4H, m), 0.90 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 19.5, 22.1, 31.6, 70.5, 70.6, 72.8, 73.8, 74.2, 76.2, 76.7, 79.3, 117.8, 118.1, 128.4, 130.2, 133.3, 134.3, 134.8, 145.2, 147.9.

***N*-Butyloxy-[3(e),4(e),5(e)]-3,4,5-triallyloxypiperidine (20).** The oxime **19** (790 mg, 1.60 mmol) was subjected to the generalized reductive cyclization procedure to give piperidine **20** (220 mg, 0.67 mmol, 42%): $R_f = 0.40$ (10% EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91 (3H, m), 5.20 (6H, m), 4.10−4,35 (6H, m) 3.64 (2H, t, $J = 6.2$ Hz,), 3.41−3.52 (4H, m), 3.20 (1H, t, $J = 11.5$ Hz), 2.38 (2H, t, $J = 11.6$ Hz), 1.43 (4H, m), 0.90 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.0, 135.5, 117.1, 116.6, 86.1, 76.6, 74.5, 72.7, 72.3, 58.2, 31.4, 19.9, 14.5. Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.22; H, 9.51; N, 4.35.

***O*-*n*-Butyl *N*-[(2*R*,3*S*,4*R*)-2,3,4-triallyloxy-5-hydroxypentyl]hydroxylamine 22**. To a solution of the oxime **18** (685 mg, 2.01 mmol) and $NaBH_3CN$ (380 mg, 6.03 mmol) in MeOH (30 mL) was added concentrated HCl (2 mL) at room temperature. The reaction mixture was stirred for 1 h and then concentrated in vacuo. The residue was purified by column chromatography (silica gel) to provide hydroxylamine **22** (668 mg, 1.94 mmol, 97%): $R_f = 0.25$ (33% EtOAc/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91 (3H, m), 5.20 (6H, m), 3.58−4.21 (15H, m), 3.21 (1H, dd, $J = 11.5$, 5.0 Hz), 2.97 (1H, dd, $J = 11.5$, 7.3 Hz), 1.45 (4H, m), 0.92 (3H, t, $J = 7.3$ Hz). Anal. Calcd for $C_{18}H_{33}NO_5$: C, 62.95; H, 9.68; N, 4.08. Found: C, 62.83; H, 9.64; N, 4.07.

Procedure for the Mitsunobu Cyclization. *N*-Butyloxy-[3(e),4(e),5(e)]-3,4,5-triallyloxypiperidine (20). To a solution of **22** (665 mg, 1.93 mmol) in anhydrous THF (100 mL) were added Ph_3P (1.02 g, 3.86 mmol) and DEAD (0.67 mL, 4.25 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature and then concentrated in vacuo. The residue was purified by silica gel column chromatography to afford **20** (470 mg, 1.45 mmol, 75%): $R_f =$ 0.60 (20% EtOAc/petroleum ether).

Generalized Deallylation Procedure. *N*-Butyloxy-[3(e),4(e),5(e)]-3,4,5-trihydroxypiperidine (6). A mixture of **20** (600 mg, 1.85 mmol), $Rh(PPh_3)_3Cl$ (120 mg, 0.13 mmol), DABCO (41 mg, 0.37 mmol), EtOH (18 mL), and water (2 mL) was refluxed for 1 h. The resultant solution was treated with 2 N HCl (20 mL) and refluxed for another hour. The reaction mixture was cooled to room temperature and washed with CH_2Cl_2 (40 mL). The aqueous layer was collected and concentrated in vacuo. The anhydrous residue was treated with a mixture of Ac_2O (1.3 mL, 13.45 mmol) and Et_3N (5 mL) in CH_2Cl_2 (25 mL) and was stirred overnight. After workup (water, CH_2Cl_2) and column chromatography purification, triacetate **23** (507 mg, 1.53 mmol) was isolated in 83% yield. Compound **23** was subjected to basic Amberlite (1 g) in MeOH (10 mL) at room temperature overnight. The resin was filtered off, and the filtrates were concentrated and dried to give **6** (314 mg, 1.53 mmol, 100%) as a white solid. **23**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.14 (2H, br), 4.99 (1H, t, $J = 9.1$ Hz), 3.55 (2H, t, $J = 6.5$ Hz), 3.42 (2H, dd, $J = 12.0$, 4.6 Hz), 2.50 (2H, t, $J = 11.5$ Hz), 1.93 (6H, s), 1.92 (3H, s), 1.38 (4H, m), 0.82 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 170.1, 74.2, 72.7, 68.5, 56.1, 31.1, 21.3, 19.8, 14.4. **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.15 (3H, br), 3.50 (7H, m), 2.46 (2H, br), 1.40 (4H, m), 0.90 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.7, 72.4, 68.8, 59.7, 31.3, 19.9, 14.5. Anal. Calcd for $C_9H_{19}NO_4$: C, 52.65; H, 9.33; N, 6.83. Found: C, 52.50; H, 9.24; N, 6.66.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the final products and intermediates (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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